Inhalation Device and Method

Cross-Reference to Related Applications

[0001] The present application is a divisional of Application No. 09/835,302, filed April 16, 2001, the entirety of which is incorporated herein by reference.

Background of the Invention

Field of the Invention

[0002] The present invention relates generally to facilitating release of powder contained in a receptacle. More specifically, the present invention relates to the administration of medication by a method and apparatus for facilitating inhalation of powder medicaments.

Related Art

[0003] In the medical field, it is often desirable to administer various forms of medication to patients. Well known methods of introducing medication into the human body include the oral ingestion of capsules and tablets, intravenous injection through hypodermic needles, and numerous others. In one method, certain medications may be inhaled into a patient's respiratory tract and lungs through the nose or mouth. Certain of these medications, such as bronchodilators, corticosteroids, etc., for the treatment of asthma and other respiratory anomalies, may be aimed at the respiratory tract directly. Others are inhaled for purposes of systemic treatment, *i.e.* for treatment of any area of the body through absorption from the respiratory tract through the lung tissue, into the deep lungs, and into the bloodstream. Each of these medications comes in a variety of forms, including fluids, which are commonly administered as an aerosol vapor or mist, as well as solids. Inhalable solids typically take the form of fine, dry powders. Specialized devices, such as inhalers, are provided to assist the patient in directing these fine powder medications into the respiratory tract.

[0004] Various types of inhalers are known for the administration of dry powder medicaments. However, each of these inhalers suffers certain drawbacks. For example, U.S. Patent No. 5,787,881 discloses an inhaler that is used with encapsulated dry powder medicaments. However, use of this device requires numerous steps and imposes a number of inconveniences on a user. For example, the medication capsules used with the device have an aperture formed therein prior to insertion into an opening in the inhaler. Therefore, there

exists a danger that an amount of medication may be lost prior to or during insertion into the device. After insertion of the capsule, use of the device requires the additional step that a cover must be closed before the medication may be inhaled.

[0005] Inhalation devices configured for use with a capsule containing some type of medicament are shown in U.S. Patent No. 4,069,819 to Valentini *et al.* ("the '819 patent") and U.S. Patent No. 4,995,385 to Valentini *et al.* ("the '385 patent"). The inhalation device described in the '385 patent was developed to overcome the drawbacks of the device described in the '819 patent. Particularly, in a large number of cases, the device described in the '819 patent experienced irregular and incomplete emptying of the capsule, thereby resulting in difficulties in properly administering the medicament in the capsule. The inhalation device described in the '385 patent attempts to overcome this deficiency by tapering the nebulization chamber toward the end surface that comprises the discharge holes. Thus, the nebulization chamber of the '385 patent is not cylindrical, but rather frusto-conical in form in an attempt to achieve regular complete emptying of the nebulization chamber. However, further improvements in the design of inhalation devices are needed to achieve a higher emitted dose. As used herein, "emitted dose" refers to the percentage of the dose of powder medicament, contained in a receptacle in the inhalation device, that is emitted from the inhalation device. Moreover, improvements are needed to achieve higher emitted doses that are consistently reproducible, *i.e.,* with low standard deviation. There is a particular need in the art for high, reproducible emitted doses at low flow rates, as well as for high dosage ranges.

[0006] Another drawback of the inhalation devices described in the '819 and the '385 patents is the piercing device that is used to puncture the capsule. Such conventional piercing devices are formed from circular stock, with the points created by pinching the stock at an angle, thereby creating a single sharp cutting edge. Drawbacks of such a design are that the point (which must puncture the capsule material) is often rounded, lessening its effectiveness as a piercing device. Moreover, burrs often form on the lower edge, which can stop the piercing device from retracting from the capsule, thereby causing a device failure. The holes formed by such a conventional piercing device are generally round, and do not have the appearance of being cut by a sharp edge. With such a conventional design, the capsule is

often crushed, rather than punctured or pierced. If such a conventional piercing device is used with brittle capsule materials such as gelatin, pieces of capsule material of a size that can be inhaled are usually broken off from the capsule. Thus, conventional piercing devices are less than optimal, particularly for brittle capsule material.

[0007] Thus, there is a need in the art for an improved method and apparatus for inhalation of dry powder medicaments. What is needed is an inhaler that provides for a higher emitted dose that is consistently reproducible with low standard deviation. Such a need is particularly acute for low flow rates, and for high dosage ranges. There is a further need in the art for an improved means for puncturing the capsule containing the medicament. The present invention, the description of which is fully set forth below, solves the need in the art for such improved methods and apparatus.

Summary of the Invention

[0008] The present invention relates to a method and apparatus for facilitating release of powder from a device. In one aspect of the invention, a device for emitting powder is provided. The device includes a first casing portion, and a second casing portion removably coupled to the first casing portion. A cylindrical chamber, defined by a straight wall of circular cross section, is coupled to the first casing portion. The chamber has a proximal end and a distal end. A ring is circumferentially coupled to an inner surface of the chamber. The ring is preferably disposed at approximately a midpoint of the chamber, or, alternatively, disposed adjacent the proximal end of the chamber. The second casing portion includes an emitter portion disposed at the proximal end of the chamber when the first and second casing portions are coupled together. The emitter portion defines at least one aperture configured to emit powder therethrough.

[0009] In another aspect of the present invention, the device is configured as an inhalation device for administering powder. In this aspect of the present invention, the emitter portion is configured as an inhalation portion so that powder is dispersed in the chamber and administered to a user through the inhalation portion. The inhalation portion may be configured as a mouth piece for inhalation through the mouth, or as a nose piece for inhalation through the nose.

[0010] In one aspect of the invention, the powder is contained in a receptacle that is disposed in the chamber. Upon puncturing the receptacle, powder is dispersed in the chamber and emitted or inhaled from the device.

[0011] In yet another aspect of the present invention, the device of the present invention includes means for puncturing the receptacle. The means for puncturing can be configured as a staple. Such a staple is preferably configured in a substantially U-shape, having two prongs. In one aspect of the present invention, each of the prongs has a square cross-section. In another aspect of the present invention, the substantially U-shaped staple includes a rounded portion and two prongs that define a non-planar inner edge and a non-planar outer edge of the staple, the staple being formed from a rectangular length having two end surfaces and four planar side surfaces that intersect to form four non-planar edges. The inner edge of the staple is configured to be one of the non-planar edges, and the outer edge of the staple is the non-planar edge that is opposite that non-planar edge. Each end surface is an angled diamond-shaped surface. In a preferred aspect, each end surface has a top point at an apex of the inner edge, and a bottom point at an apex of the outer edge, each top point forming a cutting point for one of the prongs.

[0012] In still a further aspect of the present invention, a method for dispensing powder by inhalation is provided. Such a method comprises

[0013] providing a powder inhalation device, the device comprising

[0014] a first casing portion,

[0015] a cylindrical chamber, defined by a straight wall of circular cross-section, coupled to said first casing portion, said chamber having a proximal end and a distal end and configured to receive a receptacle therein, said chamber comprising a ring circumferentially coupled to an inner surface of said chamber, and

[0016] a second casing portion removably coupled to said first casing portion, said second casing portion comprising an inhalation portion disposed at the proximal end of said chamber when said first and said second casing portions are coupled, said inhalation portion

comprising a hemispheric region defining a plurality of apertures configured to emit powder therethrough;

[0017] puncturing the receptacle to disperse powder in said chamber; and

[0018] inhaling the powder through said inhalation portion.

[0019] In one aspect of the present invention, the inhaling step is carried out by inhaling the powder through a mouthpiece into a user's mouth. Alternatively, the inhaling step may be carried out by inhaling the powder through a nose piece into a user's nose.

Features and Advantages

[0020] One feature of the present invention is that it provides high emitted doses that are consistently reproducible over a range of flow rates and dosage quantity. Advantageously, the present invention improves the emitted dose at both low flow rates and high dose ranges. A particularly advantageous feature of the present invention is its ability to operate at low flow rates, such as would be associated with a child or a person with a respiratory disease.

[0021] One advantage of the present invention is that the preferred means for puncturing used in the device is less expensive to manufacture than conventional piercing devices. Moreover, the means for puncturing of the present invention advantageously provides improved puncturing performance since less force is needed to puncture the receptacles, and fewer failures result than with conventional piercing devices.

[0022] Another advantage of the preferred means for puncturing is an improvement to the flow rate independence of the inhaler. Consequently, the powdered medicament delivered to a patient will be independent of how fast the patient breathes, thereby ensuring that a consistent dose of medicament is delivered each time.

[0023] Another advantageous feature of the present invention is the accuracy of medicament dosage delivered thereby. Since only one dosage of medication is present in the inhaler during each use, the possibility of overdose is eliminated, and the medicament need not be metered prior to delivery. A patient may simply inhale all medicament present in the device.

[0024] Because the present invention operates only under the inhalative power of the patient, the inhaler carries the additional advantage that no accessory device, such as a compressed air cylinder or other propellant, needs to be used in conjunction with the present invention.

[0025] Another advantage of the present invention is that during inhalation, the medicament is subjected to mixing in the dispersion chamber. This helps to ensure that the medicament exiting the inhaler and entering the patient's respiratory system is in the form of a fine dry powder, facilitating medicament deposition in the lungs. In addition, inhalation of finer powders is typically more comfortable for the patient.

[0026] Still another advantage of the present invention is that it can be used with individuals who cannot breathe hard, such as a child or an asthmatic, or individuals who are sleeping or in a coma.

[0027] Yet another advantage of the apparatus of the present invention is that it is reusable. To reuse, a patient removes the emptied receptacle, and replaces it with a fresh receptacle filled with the proper dose of medicament.

Brief Description of the Figures

[0028] The present invention is described with reference to the accompanying drawings. In the drawings, like reference numbers indicate identical or functionally similar elements.

[0029] FIG. 1 is a front view of one embodiment of a device of the present invention;

[0030] FIG. 2 is a cross-section of the device shown in FIG. 1 along line 2-2;

[0031] FIG. 3 is an enlarged partial cross-section of one embodiment of a dispersion chamber of the present invention;

[0032] FIG. 4 is an enlarged partial cross-section of another embodiment of a dispersion chamber of the present invention showing one location for a ring in the dispersion chamber;

[0033] FIG. 5 is an enlarged partial cross-section of another embodiment of a dispersion chamber of the present invention showing another location for a ring in the dispersion chamber;

[0034] FIG. 6 is an enlarged partial cross-section of another embodiment of a dispersion chamber of the present invention showing another location for a ring in the dispersion chamber;

[0035] FIG. 7A is a top view of a preferred embodiment of a staple suitable for use with the device of the present invention;

[0036] FIG. 7B is a front view of the embodiment shown in FIG. 7A;

[0037] FIG. 7C is a side view of the embodiment shown in FIG. 7A;

[0038] FIG. 7D is an isometric view of the embodiment shown in FIG. 7A;

[0039] FIG. 8 shows the puncture obtained with the staple shown in FIGS. 7A through 7D;

[0040] FIG. 9A shows a partial view of another embodiment of a staple suitable for use with the device of the present invention;

[0041] FIG. 9B illustrates the puncture obtained with the staple shown in FIG. 9A;

[0042] FIG. 10 is a bar graph illustrating emitted dose at flow rates of 20 L/min (left bar), 40 L/min (center bar), and 60 L/min (right bar) for four dispersion chamber configurations;

[0043] FIG. 11 is a bar graph illustrating emitted dose at low flow rates for devices with varying numbers of slits;

[0044] FIG. 12 is a bar graph showing a comparison of mass fraction distributions obtained for 6 mg (left bar) and 50 mg (right bar) fill weights;

[0045] FIG. 13 is a graph showing glucose levels (mg/dL) in beagle dogs after administration of insulin using an aerosol generator and a device of the present invention with the low ring configuration substantially as shown in FIG. 4;

[0046] FIG. 14 is a bar graph illustrating the percentage emitted dose as a function of air volume; and

[0047] FIG. 15 is an exploded cross-sectional view of an alternate embodiment of a device of the present invention.

Detailed Description of the Preferred Embodiments

Overview

[0048] The present invention provides an improved method and apparatus for facilitating release of powder. In a preferred embodiment, the powder is contained in a receptacle. As used herein, the term "receptacle" includes but is not limited to, for example, a capsule, blister, film covered container well, chamber, and other suitable means of storing a powder known to those skilled in the art. The present invention will be described below in the context of a method and apparatus for dispensing dry powder medicaments for inhalation by a patient. However, it should be apparent to one skilled in the art that the invention is not limited to such an exemplary embodiment, and could be used for other purposes.

[0049] As will be described in more detail below, an apparatus of the present invention is an inhaler that includes a chamber. In one embodiment, the chamber is configured to receive the receptacle containing the medicament. To improve the emptying of the receptacle and provide a higher reproducible emitted dose, the chamber includes a ring circumferentially coupled to an inner surface of the chamber. The ring is preferably disposed at approximately a midpoint of the chamber, or alternatively, adjacent the proximal end of the chamber. In proper use, air will exit the inhaler carrying a full dose of medicament in the form of a fine, dry powder.

[0050] The inhaler of the present invention is preferably configured with a means for puncturing the receptacle that improves puncturing performance, particularly with brittle receptacle material. The means for puncturing the receptacle of the present invention is preferably configured as a substantially U-shaped staple with two prongs, each prong having a sharp point and two cutting edges. In one embodiment of the present invention, each prong has a square cross-section, with the staple material being bent around a face so that the innermost part of the U-shaped staple is flat. In another embodiment of the present invention, the staple material is rotated 45 degrees so that it is bent around an edge so that the innermost part of the U-shaped staple is an edge. In such an embodiment, the end surface of each prong is an angled diamond-shaped surface.

[0051] The methods of the present invention use an inhaler to dispense powder by inhalation. As will be discussed in greater detail below, a user operates the device to puncture the receptacle to disperse powder in the chamber, and inhales the powder through the inhalation portion.

Inhaler and Associated Method of the Present Invention

[0052] A front view of one embodiment of an inhalation device **100** of the present invention is shown in FIG. 1. The rear view of device **100** is substantially identical to the front view. Device **100** includes a first or lower casing portion **120** and a second or upper casing portion **130** removably coupled to first casing portion **120**. Upper casing portion **130** and lower casing portion **120** include a flattened region **132** and **122**, respectively, for ease of gripping the casing for use by a patient. Lower casing portion **120** preferably includes an outer casing **126** and an inner casing **124** movably received within outer casing **126**. A removable cap **110** is provided at the user or inhalation end of the device.

[0053] Preferred materials for device **100** include Food and Drug Administration (FDA) approved, USP tested plastics. Preferably, device **100** is manufactured using an injection molding process, the details of which would be readily apparent to one skilled in the art.

[0054] FIG. 2 is a cross-section of device **100** shown in FIG. 1 along line 2-2. As shown in FIG. 2, device **100** includes an inhalation or emitter portion **220**. Inhalation portion **220** comprises a hemispheric region **222** that defines a plurality of apertures **224**. It should be understood that the present invention is not limited to a particular number of apertures **224**, and can be configured such that at least one aperture **224** is provided. An inhalation piece **226** is provided to allow for inhalation of the medicament by a user. Inhalation piece **226** can be configured as a mouth piece for inhalation through a user's mouth. Alternatively, inhalation piece **226** can be configured as a nose piece for inhalation through a user's nose.

[0055] Device **100** includes a cylindrical chamber **210** that is defined by a straight wall **212** of circular cross-section. Chamber **210** has a proximal end **214** and a distal end **216**. A plurality of slits **218** are defined by wall **212**, and are configured for introducing air into chamber **210** to disperse powder released from a capsule **219**. It should be understood that the present invention is not limited to a particular number of slits **218**, and can be configured

such that at least one slit **218** is provided. Powder released from capsule **219** is dispersed in chamber **210** and inhaled through apertures **224** and inhalation piece **226** by the user.

[0056] In other embodiments of the invention, receptacles other than capsules are used, such as blisters and film covered container wells as is known in the art. In one embodiment, the volume of the receptacle is at least about 0.37 cm^3. In another embodiment, the volume of the receptacle is at least about 0.48 cm^3 . In yet another embodiment, the receptacles have a volume of at least about 0.67 cm^3 or 0.95 cm^3 . In one embodiment of the invention, the receptacle is a capsule designated with a capsule size 2, 1, 0, 00, or 000. Suitable capsules can be obtained, for example, from Shionogi (Rockville, MD). Blisters can be obtained, for example, from Hueck Foils, (Wall, NJ).

[0057] The receptacle encloses or stores particles, also referred to herein as powders. The receptacle is filled with particles in a manner known to one skilled in the art. For example, vacuum filling or tamping technologies may be used. Generally, filling the receptacle with powder can be carried out by methods known in the art. In one embodiment of the invention, the particle or powder enclosed or stored in the receptacle have a mass of about 5 milligrams (mg). Preferably the mass of the particles stored or enclosed in the receptacle is at least about 10 mg.

[0058] In one embodiment of the present invention, particles used with the device have a tap density of less than about 0.4 g/ cm^3 . Particles having a tap density of less than about 0.4 g/ cm^3 are referred to herein as "aerodynamically light". In a preferred embodiment, the particles have a tap density of near to or less than about 0.1 g/ cm^3 . Tap density is a measure of the envelope mass density characterizing a particle. The envelope mass density of particles of a statistically isotropic shape is defined as the mass of the particle divided by the minimum sphere envelope volume within which it can be enclosed. Features that can contribute to low tap density include irregular surface texture and hollow or porous structure. Particularly preferred particles and powders are described in U.S. Patent Nos. 6,136,295, 5,985,309, 5,874,064, and 5,855,913, and U.S. Patent Appl. No. 09/591,307, filed June 9, 2000 entitled "High Efficient Delivery of a Large Therapeutic Mass Aerosol", the entirety of each of the foregoing patents and patent applications is hereby incorporated herein by reference.

[0059] Device **100** includes a means for puncturing **230** that is used to puncture capsule **219** to release powder contained therein into chamber **210**. In the embodiment shown in FIG. 1, means for puncturing **230** is configured as a substantially U-shaped staple having two prongs **232**. In this embodiment, each of prongs **232** is configured with a square cross-section **234**, thereby providing a sharp point and two cutting edges. This will be discussed in more detail below with respect to FIGS. 9A and 9B. As discussed in more detail below, device **100** could alternatively be configured with the puncturing implement shown in FIGS. 7A through 7D. As can be readily appreciated by one skilled in the art, the present invention is not limited to use of a substantially U-shaped staple as the means for puncturing the capsule. Alternatively, one, or a plurality of, straight needle-like implements could be used. Preferably, the puncturing implement is configured to puncture at least two holes in the capsule.

[0060] Means for puncturing **230** is preferably configured to be movable between a non-puncturing position (as depicted in FIG. 1) and a puncturing position. In the puncturing position, prongs **232** pierce or puncture capsule **219** to make holes therein. In a preferred embodiment, a means for biasing is provided that biases the means for puncturing **230** in the non-puncturing position. In the embodiment shown in FIG. 2, the means for biasing is configured as a spring **242** that biases the substantially U-shaped staple in the non-puncturing position.

[0061] As noted with respect to FIG. 1, device **100** includes inner casing **124** and outer casing **126**. As shown in FIG. 2, a spring **244** is disposed in lower casing portion **120** that biases inner casing **124** in an outward position. Upon compression of spring **244**, inner casing **124** moves from the outward position to an inward position, thereby drawing lower casing portion **120** toward upper casing portion **130**. Compression of spring **244** also causes compression of spring **242**, thereby causing means for puncturing **230** to move to the puncturing position. Upon release of compression, springs **242** and **244** return to their biased state, thereby returning means for puncturing **230** to its non-puncturing position, and inner casing **124** to its outward position.

[0062] A pair of flanges **252** is disposed on first casing portion **120**. A pair of grooves **254** is disposed on second casing portion **130** so that flanges **252** can be received within grooves **254** to thereby couple the first and second casing portions. Preferably, the first and second

casing portions are coupled with a friction-fit engagement. A friction-fit engagement can be achieved using the groove and flange arrangement depicted in FIG. 2. Other alternative configurations for a friction-fit engagement would be readily apparent to one skilled in the art.

[0063] FIG. 3 is an enlarged partial cross-section of one embodiment of chamber **210**. In the embodiment shown in FIG. 3, chamber **210** does not contain a ring disposed on an inner surface, and an inner diameter of chamber **210** is depicted as "X". Such a configuration may be referred to herein as a "straight" chamber configuration.

[0064] FIG. 4 is an enlarged partial cross-section of another embodiment of chamber **210**. In the embodiment shown in FIG. 4, a ring **400** is circumferentially coupled to an inner surface of chamber **210**. An inner diameter of ring **400** is depicted as "Y", and is less than inner diameter X of chamber **210**. In the embodiment shown in FIG. 4, ring **400** is disposed at approximately a midpoint of chamber **210**. Such a configuration may be referred to herein as a "low" ring position or "low" chamber configuration. As shown in FIG. 4, in the low ring position, ring **400** is disposed adjacent slits **218**. The ring position is measured by the distance from the top of hemispheric region **222** to the bottom edge of ring **400**. This distance is depicted as "Z". The following dimensions are provided as exemplary dimensions of a device of the present invention. It should be understood by one skilled in the art that the present invention is not limited to the dimensions provided herein, or to any particular dimensions. In one embodiment of the chamber **210** shown in FIG. 4, diameter X is 0.47 in., diameter Y is 0.38 in., and distance Z is 0.49 in.

[0065] FIG. 6 is an enlarged partial cross-section of another embodiment of chamber **210**. In the embodiment shown in FIG. 6, ring **400** is circumferentially coupled to an inner surface of chamber **210**. An inner diameter of ring **400** is depicted as "Y", and is less than inner diameter X of chamber **210**. In the embodiment shown in FIG. 6, ring **400** is disposed adjacent the proximal end of chamber **210**. Such a configuration may be referred to herein as a "high" ring position or a "high" chamber configuration. The ring position is measured by the distance from the top of hemispheric region **222** to the bottom edge of ring **400**. This distance is depicted as "Z". The following dimensions are provided as exemplary dimensions of a device of the present invention. It should be understood by one skilled in the art that the

present invention is not limited to the dimensions provided herein, or to any particular dimensions. In one embodiment of the chamber **210** shown in FIG. 6, diameter X is 0.47 in., diameter Y is 0.38 in., and distance Z is 0.29 in.

[0066] FIG. 5 is an enlarged partial cross-section of another embodiment of chamber **210**. In the embodiment shown in FIG. 5, ring **400** is circumferentially coupled to an inner surface of chamber **210**. An inner diameter of ring **400** is depicted as "Y", and is less than inner diameter X of chamber **210**. In the embodiment shown in FIG. 5, ring **400** is disposed between the low ring position of FIG. 4 and the high ring position of FIG. 6. Such a configuration may be referred to herein as a "mid" ring position or "mid" chamber configuration. The ring position is measured by the distance from the top of hemispheric region **222** to the bottom edge of ring **400**. This distance is depicted as "Z". The following dimensions are provided as exemplary dimensions of a device of the present invention. It should be understood by one skilled in the art that the present invention is not limited to the dimensions provided herein, or to any particular dimensions. In one embodiment of the chamber **210** shown in FIG. 5, diameter X is 0.47 in., diameter Y is 0.38 in., and distance Z is 0.39 in.

[0067] In one embodiment of the present invention, ring **400** is integral with chamber **210**. In such an embodiment, ring **400** and chamber **210** are formed as a unit, such as through an injection molding, extrusion or a casting process. In another embodiment of the present invention, ring **400** is attached to the inner surface of chamber **210** in a manner known to those skilled in the art, such as through the use of glue or other type of adhesive, or by using an attaching device such as a pin or screw, etc. Preferably, the casing of device **100** is made from a material that can be injection molded, such as a plastic material (preferably FDA approved, USP tested). As would be readily apparent to one skilled in the art, the material is preferably durable, easy to clean, and non-reactive with powder medicaments.

[0068] An exploded cross-sectional view of an alternate embodiment of a device **1500** of the present invention is shown in FIG. 15. Device **1500** includes a first or lower casing portion **1540** and a second or upper casing portion **1550** removably coupled to first casing portion **1540**. First and second casing portions **1540** and **1550** are coupled through the use of a flange **1552** and a groove **1554**. Preferred materials for device **1500** include Food and Drug

Administration (FDA) approved, USP tested plastics. Preferably, device **1500** is manufactured using an injection molding process, the details of which would be readily apparent to one skilled in the art.

[0069] Device **1500** includes an inhalation or emitter portion **1520**. Inhalation portion **1520** comprises a hemispheric region **1522** that defines a plurality of apertures **1524**. It should be understood that the present invention is not limited to a particular number of apertures **1524**, and can be configured such that at least one aperture **1524** is provided. An inhalation piece **1526** is provided to allow for inhalation of the medicament by a user. Inhalation piece **1526** can be configured as a mouth piece for inhalation through a user's mouth. Alternatively, inhalation piece **1526** can be configured as a nose piece for inhalation through a user's nose.

[0070] Device **1500** includes a cylindrical chamber **1510** that is defined by a straight wall **1512** of circular cross-section. A plurality of slits **1518** are defined by wall **1512**, and are configured for introducing air into chamber **1510** to disperse powder released from, for example, capsule **219** as illustrated in FIG. 2. It should be understood that the present invention is not limited to a particular number of slits **1518**, and can be configured such that at least one slit **1518** is provided. Powder released from capsule **219** is dispersed in chamber **1510** and inhaled through apertures **1524** and inhalation piece **1526** by the user.

[0071] As would be readily apparent to one skilled in the art, device **1500** can be configured with means for puncturing and means for biasing in a manner similar to that described above with respect to the embodiment shown in FIGS. 1 and 2. Means for puncturing are described in more detail below with respect to FIGS. 7A through 7D, 8, 9A, and 9B. Moreover, device **1500** can be configured with the chamber designs described above with respect to FIGS. 3-6.

[0072] FIG. 10 is a bar graph illustrating emitted dose at flow rates of 20 L/min (left bar), 40 L/min (center bar), and 60 L/min (right bar) for a total volume of 2L for four dispersion chamber configurations (standard deviations shown; sample size n=3). The flow rates were measured with a flow meter. The emitted dose measurement involved placing a capsule into four embodiments of the inhaler of the present invention for actuation into an emitted dose (ED) measurement apparatus. The ED apparatus included a powder filter and a filter holder. The powder collected by the ED apparatus was quantified by fluorescence spectrophotometry. The straight configuration is shown in FIG. 3; the low configuration is

shown in FIG. 4; the mid configuration is shown in FIG. 5; and the high configuration is shown in FIG. 6. As can be seen from FIG. 10, each of the low, mid, and high configurations demonstrated a higher emitted dose at each of the three flow rates than the straight (no ring) configuration. Thus, the ring configuration of the present invention provides an improvement over conventional chamber designs without a ring, such as those shown in the '819 and '385 patents. At each of the flow rates shown in FIG. 10, the low configuration produced a higher emitted dose and a lower standard deviation than the mid and high configurations.

[0073] FIG. 11 is a bar graph illustrating emitted dose at low flow rates for devices with varying numbers of slits **218**. A flow rate of less than about 15 L/min will be referred to herein as a "low flow rate." The measurements were taken at a flow rate of 5 L/min, with a volume of 67 cc and a 15 mg dosage. As show in FIG. 11, by decreasing the number of slits **218**, the emitted dose increases so that the device of the present invention successfully delivers a high emitted dose at low flow rate over multiple (ten) actuations. Thus, the device of the present invention achieves a high emitted dose at low flow rates that is consistently reproducible with low standard deviation.

[0074] Experiments were conducted to evaluate the emitted dose as a function of air volume drawn through the inhaler. The inhaler was operated at a constant flow rate of 30 L/min for a 5 mg dose. The volume of air through the inhaler was varied by varying the actuation time. Volumes of 0.5, 1.0, 1.5, 2.0 and 3.0 L were investigated. FIG. 14 shows the percentage emitted dose as a function of air volume (n=3, standard deviations shown). The emitted dose remained constant across the range of volumes and was consistently reproducible with low standard deviation.

[0075] In the embodiments having the inner diameter X of chamber **210** of 0.47 in. and the inner diameter Y of ring **400** of 0.38 in., the ratio of the inner diameter of the ring to the inner diameter of the chamber is about 0.8. By modifying the inner diameters of the ring and the chamber, it is possible to optimize the emitted dose at varying flow rates. As reported in Annals of the ICRP, Human respiratory tract model for radiological protection, 24 (1-3), Elsevier Science, Inc., New York, 1994, the flow rate for a tidal breathing seated adult male is 300 mL/s (18 L/min) for a volume of 750 mL. In one embodiment of a device of the present invention optimized for low flow rates (less than about 15 L/min), inner diameter X

of chamber **210** is 0.33 in. and inner diameter Y of ring **400** is 0.30 in. In such an embodiment, the ratio of the inner diameter of the ring to the inner diameter of the chamber is about 0.9. Preferably, the ratio of the inner diameter of the ring to the inner diameter of the chamber is about 0.9 or less.

[0076] The device of the present invention can also be optimized for varying dosage ranges. One way to do so is to vary the dimensions of chamber **210** to accommodate varying sizes of capsules. For example, a chamber having an inner diameter X of 0.33 in., inner diameter Y of 0.30 in., and distance Z of 0.57 in. can be used with size 2 and size 00 capsules. It should be readily apparent to one skilled in the art that chamber **210** can be scaled to accommodate varying capsule sizes, and to accommodate those capsule sizes at varying flow rates.

[0077] The device of the present invention can be used with varying dosage ranges. A highly dispersible powder was prepared and loaded into capsules to obtain a large pre-metered dose (50 mg) and a smaller pre-metered dose (6 mg). The particle size characteristics of the powder were as follows: Dg=10.6μm; ρ=0.11 g/cc; and Da=3.5 μm, where Dg is the mean geometric diameter, ρ is the powder density, and Da is the mean aerodynamic diameter. The aerodynamic particle size distributions were characterized using a multistage liquid impinger that extracted air at 60 L/min after actuating the inhaler device (D). As shown in FIG. 12, the mass fraction was measured at D, the induction port (IP) of the impactor, stages S1-S4, and the filter cutoff (SF). Size 2 capsules were used for the 6 mg dose and size 000 capsules were used for the 50 mg dose. FIG. 12 shows the results comparing the two particle size distributions obtained for the 6 mg (left bar) and 50 mg (right bar) doses. "ED" used on the graph refers to emitted dose, and FPM used on the graph refers to fine particle mass (estimate of the mass that would deposit in the lungs). The fine particle fraction <6.8 μm relative to the total dose (FPF_{TD} <6.8 μm) for the 6 and 50 mg doses were 74.4% and 75.0%, respectively. Similar aerodynamic particle size distributions were obtained for both doses.

[0078] FIG. 13 is a graph showing glucose (mg/dL) in beagle dogs after administration of human insulin using an aerosol generator and a device of the present invention with the low ring configuration substantially as shown in FIG. 4. The generator is a device with proven ability for forming a respirable aerosol that results in deposition of powder in dog lungs. Metered powder is presented to a chamber where the powder is dispersed by a high velocity

jet of air. The dispersed powder is directed toward a baffle to separate large agglomerates before inhalation by the dog. The pharmakodynamic profile shown in FIG.13 confirms that the device of the present invention produces a pattern of powder deposition similar to the aerosol generator.

[0079] The dogs were anesthetized for the dosing procedure. A forced maneuver was used with dogs being ventilated at 75% of their vital capacity (approximately 100 cc/s or 6 L/min for a duration of 1 second). A 4 second breath-hold was applied at the end of each inhalation. A physically smaller device was used with the low ring configuration to facilitate administration. The device performed well at the low flow rate with the anesthetized dogs using the forced maneuver. Based on these results, such a device could be used with a sleeping person or a person having breathing problems, such as from chronic obstructive pulmonary disease (COPD).

[0080] As can be seen from the description above, the device of the present invention relies upon the breath of the user to drive the inhalation process, yet the device is configured to work successfully at low flow rates. As such, the device of the present invention has particular suitability for use with individuals who cannot breath hard, such as a child, an individual with respiratory disease, or individuals who are sleeping or in a coma.

[0081] Turning now to FIGS. 7A through 7D, a preferred embodiment of a staple suitable for use in the present invention is shown. The staple preferably comprises a rectangular length of material that has four planar side surfaces **730**. Each planar side surface intersects with two other planar side surfaces to create a total of four non-planar edges **736**. The staple is preferably bent into a substantially U-shaped configuration, thereby having a rounded portion and two prongs **732**. The prongs **732** terminate at two end surfaces **731**. As best seen in FIGS. 7A, 7C and 7D, end surfaces **731** are diamond-shaped.

[0082] The diamond-shaped end surfaces are created by bending the material about a non-planar edge. This configuration is best shown in FIGS. 7B and 7D. As can be seen, each prong **732** has an inner surface **738** that comprises one of the non-planar edges and an outer surface **740** that comprises the opposite non-planar edge. The inner surface **738** of each prong **732** terminates at the uppermost portion **737** of the diamond-shaped end surface,

thereby creating a cutting edge for the prong. The outer surface **740** of the prong **732** terminates at the lowermost portion **735** of the diamond-shaped end surface.

[0083] FIGS. 9A and 9B depict another embodiment of a staple suitable for use in the present invention. This staple preferably comprises a rectangular length of material that has four planar side surfaces. Each planar side surface intersects with two other planar side surfaces to create a total of four non-planar edges. The staple is preferably bent into a substantially U-shaped configuration, thereby having a rounded portion and two prongs. The prongs terminate at two end surfaces that have a square shape.

[0084] The square-shaped end surfaces are created by bending the material about a planar side surface. As shown in FIG. 9A, each prong has an inner surface that comprises one of the planar side surfaces and an outer surface that comprises the opposite planar side surface. The inner surface of each prong terminates at the uppermost portion of the square-shaped end surface, thereby creating a cutting edge for the prong. The outer surface of the prong terminates at the lowermost portion of the square-shaped end surface.

[0085] FIG. 9B illustrates a puncture obtained from using the staple depicted in FIG. 9A. As shown, the holes formed by this staple have the appearance of being cut with a sharp edge. In addition, the material removed to create the hole is peeled back and remains well attached to the capsule; thereby preventing the capsule material from being inhaled by the user when the powder medicament is being dispensed.

[0086] FIG. 8 illustrates a puncture obtained from using the staple depicted in FIGS. 7A-7D. The holes formed by the staple appear to be cut with a sharp edge, and the excess material is peeled back. In testing, the effort required to puncture the capsule is lower than circular section staples, and approximately the same as a square section staple. However, during testing, no instances were noted of crushed or otherwise mispunctured capsules. These staples are extremely inexpensive to produce, approximately one-third the cost of square section staples such as those depicted in FIG 9A.

[0087] In addition to improved puncturing performance, drug delivery from capsules punctured with the staple depicted in FIGS. 7A-7D is greatly improved. The Emitted Dose (ED) and Fine Particle Fraction (FPF) of a test powder was measured at both 20 and 60 Liters

per minute (LPM). In all cases, the aerosol emitted from capsules punctured with the diamond section staple of FIGS. 7A-7D was improved over a conventional circular stock staple. Most significantly, the FPF of powder delivered at 20 liters per minute was improved almost to the level of the FPF at 60 liters per minute.

[0088] The present invention also relates to a method for dispensing powder medicaments to a user through the various embodiments of the disclosed inhalation device. In such a method, a receptacle containing the powder medicament, *e.g.*, a capsule **219**, is placed or formed into cylindrical chamber **210**. When the user compresses the inhalation device, staple **230** is moved toward capsule **219** thereby puncturing capsule **219** to cause the release of powder into chamber **210**. After release into the chamber, the powder is then inhaled by the user through apertures **224** and inhalation piece **226**. As noted, inhalation piece **226**, can be configured as either a mouth piece or a nose piece. For subsequent uses, the user merely replaces emptied capsule **219** with another capsule **219** that contains a new supply of power medicament. Alternatively, powder medicament is injected into a permanent receptacle that is formed into chamber **210**.

Conclusion

[0089] While various embodiments of the present invention have been described above, it should be understood that they have been presented by way of example only, and not limitation. For example, the present invention is not limited to the physical arrangements or dimensions illustrated or described. Nor is the present invention limited to any particular design or materials of construction. As such, the breadth and scope of the present invention should not be limited to any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.